REMARKS

In the Office Action, dated April 1, 2009, the Examiner states that Claims 1-30, 44-53, 65 and 81 are pending, Claims 1-30, 45-48, 50-53, 65 and 81 are withdrawn, and Claims 44 and 49 are rejected. By the present Amendment, Applicant amends the specification, the claims, and the drawings.

At the outset, Applicant indicates that Claims 1-30, 45-48, 50-53, 65 and 81 are cancelled without prejudice or disclaimer of the subject matter thereof. Claims 31-43, 54-64 and 66-80 were previously cancelled. Applicants reserve the right to pursue any subject matter removed in these amendments in one or more divisional and/or continuation applications. Claim 82 is new and finds support, for example, at page 41, line 10, of the present specification. Claim 83 is new and finds support, for example, at page 43, lines 19-20, of the present specification. Accordingly, Applicant respectfully asserts that no new matter has been added.

Drawing Figures

Drawing Figures 9, 10 and 11 are objected to because Figures 9, 10, and 11 have multiple panels/pages, which should be labeled with the same number, followed by a capital letter. Applicant has submitted amended drawing figures herewith the present amendment. Specifically, the pages of Figure 9 (15/25 – 17/25) have been amended such that they are labeled as Fig. 9A, 9B, and 9C, respectively. The pages of Figure 10 (18/25 – 19/25) have been amended such that they are labeled as Fig. 10A and 10B, respectively, and the pages of Figure 11 (20/25 – 22/25) have been amended such that they are labeled as Fig. 11A, 11B, and 11C, respectively. The specification has also been updated accordingly to refer to the amended drawing figure labels. Accordingly, Applicant respectfully requests withdrawal of the present objection to the drawing figures.

Specification

The specification is objected to because the Office Action does not consider that the title is clearly indicative of the invention to which the claims are directed. Applicant respectfully indicates that the title is currently amended such that it is clearly indicative of the invention to which the claims are directed. Accordingly, Applicant respectfully requests withdrawal of the objection to the title.

Claim rejections 35 USC § 112, 2nd paragraph

Claims 44 and 49 are rejected under 35 USC § 112, 2nd paragraph, as being indefinite.

Specifically, Claim 44 is rejected as being allegedly incomplete for omitting essential steps. Without conceding the propriety of the rejection, Applicant indicates that Claim 44 has been amended to recite a comparison step.

Claim 44 has also been rejected for allegedly lacking a step that relates back to the preamble. Claim 44 has been amended to recite "a method of identifying a compound for the treatment of pain" in the preamble, and step (c) which recites "identifying a compound for the treatment of pain on the basis of said comparison" has been added.

Claim 44 has been further rejected on the grounds that there is insufficient antecedent basis for the expression "said intracellular chloride level." Applicant respectfully indicates that Claim 44 is currently amended to add proper antecedent basis for this phrase.

In view of the foregoing remarks/amendments, Applicant respectfully submits that instant Claim 44, and in turn dependent Claim 49, are not indefinite. Withdrawal of the rejection under 35 USC § 112, 2nd paragraph, is therefore respectfully requested.

Claim rejections 35 USC § 112 1st paragraph

Claims 44 and 49 are rejected under 35 USC § 112, 1st paragraph, as failing to comply with the enablement requirement.

Initially, Applicant respectfully submits that the rejections set forth in Items 17 and 18 of the Office Action are now moot in view of the claim amendment discussed above.

The Office Action further alleges that although the claimed methods could identify a test compound that decreases intracellular chloride levels in a cell, one skilled in the art would not be able to predict, with any level of certainty, whether or not the compound would actually be useful for treating pain. The Office Action further comments that, while the specification establishes a nexus between the activity and expression of the chloride transporter KCC2 and pain, the claims do not require that the cell actually express said KCC2 transporter. Applicants respectfully traverse the objection and submit the following:

First, Applicant respectfully indicates that Claim 44 has been amended to

recite "a cell expressing a CNS chloride transporter."

Applicant submits that the instant inventors were the first to establish a nexus between CNS chloride levels and pain. Indeed, the first results described in the application (see for example the paragraph bridging pages 52 and 53) relate to the determination of anion reversal potential (E_{anion}) of neurons of PNI rats (i.e., rats that were subjected to peripheral nerve injury) and their comparison to the anion reversal potential of corresponding neurons of naïve rats. In these studies, a decrease in E_{anion} (i.e., a shift of E_{anion} to a less negative potential) was observed in neurons of PNI rats relative to those of naïve rats (see, e.g., Figs. 1B-1D), thus identifying a difference between intracellular chloride levels of neurons of PNI rats versus those of naïve rats. As such, the instant inventors first established a nexus between CNS chloride levels and pain, their initial studies being carried out in such a way that their experimental design was independent of any role of a particular chloride transporter.

To further study the observed changes in CNS chloride associated with pain, the instant inventors then studied chloride transport in these neurons. To carry out such further studies, a representative CNS chloride transporter was chosen, namely, the K^+-Cl^- cotransporter 2 (KCC2), which is an outwardly directed chloride transporter (i.e., its induction results in lower intracellular chloride, whereas its inhibition results in higher intracellular chloride. These further studies determined that the decrease in E_{anion} observed in the initial studies correlates with a change in chloride transporter expression and activity. Specifically, studies relating to KCC2, which was studied as a representative chloride transporter, revealed that KCC2 inhibition (via pharmacological blockade or antisense approaches) resulted in a decrease in nociceptive threshold (Fig. 4), consistent with the E_{anion} results.

To further validate their demonstration that changes in CNS chloride levels are associated with pain, the instant inventors utilized an experimental design to decrease CNS intracellular chloride levels, again using the representative chloride transporter KCC2 to effect such a decrease in CNS intracellular chloride, more particularly by increasing the activity of the outwardly directed transporter KCC2. The results show that increasing the activity of KCC2 (which promotes chloride efflux and thus leads to a decrease in intracellular chloride levels) by various means leads to an increase in nociceptive threshold in PNI rats (Figs. 8, 16 and 17). In summary, it was determined that reversing the shift in E_{anion} observed in PNI neurons, i.e., decreasing

CNS intracellular chloride levels, reverses hyperalgesia/allodynia following peripheral nerve injury and increases nociceptive threshold, and can therefore by used for the treatment of pain.

Applicant respectfully submits that KCC2 is only a representative CNS chloride transporter whose activity may be modulated to decrease intracellular chloride levels in a cell and in turn to treat pain, and that the skilled person would be able to predict based on these results that other means of chloride modulation, e.g., by modulating the activity of any other chloride transporters, may also be used to decrease intracellular chloride and in turn can be used to treat pain. Indeed, recent reports have shown that specific inhibition of the activity of the inwardly (i.e., which normally effects chloride influx) directed Na^+,K^+,$2Cl^-$ type I cotransporter (NKCCI) using bumetanide (1) decreases referred, abdominal allodynia evoked by an intracolonic capsaicin injection (Pitcher *et al.*, *Molecular Pain* (2007) **3**: 17, copy enclosed), and (2) increases hindpaw thermal withdrawal latency time following spinal cord injury (Cramer *et al.*, *Molecular Pain* (2008) **4**: 36, copy enclosed). Therefore, it has been shown that the common result of a decrease in intracellular chloride effected by modulating different chloride transporters (KCC2 and NKCCI) which act by different mechanisms (chloride efflux versus chloride influx) by different approaches in view of their different mechanisms (via induction of activity and in turn chloride efflux in the case of KCC2; and via inhibition of activity and in turn chloride influx in the case of NKCCI), can be used for the treatment of pain. Applicant thus respectfully submits that the skilled person would be able to predict, based on a decrease in intracellular chloride in a cell expressing a CNS chloride transporter, that a compound would be useful for treating pain.

The Office Action further rejects Claims 44 and 49, commenting on the aspect of prevention. Without conceding the propriety of the foregoing rejection, Claim 44 has been amended and no longer recites "prevention."

Applicant respectfully submits that the present specification provides suitable guidance to the skilled person to practice the claimed method. A detailed description of the materials, steps and/or conditions suitable for performing the method is provided in the specification, for example, from page 39, line 26 to page 43, line 21 of the specification and in the working examples. More specifically:

- details concerning the cells which may me used are provided, for

example, at page 40, lines 7-33;

- details concerning the screening procedure are provided, for example, at page 41, lines 14-28;
- details concerning the measurement of intracellular chloride levels are provided, for example, at page 43, lines 15 to 21 and in Example I (page 48, lines 6-30).

In view of the foregoing, Applicant respectfully submits that the specification enables one skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with the present claims, in compliance with 35 USC § 112, 1st paragraph. Reconsideration and withdrawal of the rejection under 35 USC § 112, 1st paragraph, is respectfully requested.

In light of the foregoing response, all the outstanding objections and rejections are considered overcome. Applicant respectfully submits that this application should now be in condition for allowance and respectfully requests favorable consideration.

Respectfully submitted,

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Date

Attorney for Applicant
Eric D. Babych
c/o Ladas & Parry LLP
224 South Michigan Avenue
Chicago, Illinois 60604
(312) 427-1300
Reg. No. 57,542